REMARKS

Rejection of Claims and Traversal Thereof

In the September 22, 2010 Final Office Action:

Claims 1, 3, 5-7 and 10 were rejected under 35 U.S.C. §103(a) as being unpatentable over Hancock (US Pub. No. 2002/0019345, hereinafter Hancock) in view of Baba, et al (*Proc. Natl. Acad. Sci. USA*, May 1999, vol. 96 pp. 5698-5703, hereinafter Baba); and

Claims 1, 3, 5-7 and 10 were rejected under 35 U.S.C. §103(a) as being unpatentable over Vezina (WO94/05300, hereinafter Vezina) in view of Baba.

These rejections are hereby traversed and reconsideration of the patentability of the pending claims is therefore requested in light of the following remarks.

Rejection under 35 U.S.C. §103(a)

1. Claims 1, 3, 5-7 and 10 were rejected under 35 U.S.C. §103(a) as being unpatentable over Hancock in view of Baba. Applicants insist that such a combination does not establish a *prima facie* case of obviousness.

Applicants' claimed invention is a composition with three important elements:

1) at least one G1 phase arresting compound;
2) at least one HIV viral entry inhibitor that inhibits entry of HIV to mononuclear cells; and
3) the G1 phase arresting compound is in an amount sufficient to increase concentrations of extracellular β-chemokines, wherein the chemokines comprise MIP-1α, MIP-1β and RANTES.

Hancock describes a composition that includes an antagonist of CCR5 and an immune suppressant, wherein the composition **is used to reduce graft rejections**. Notably, Hancock is concerned about an increase or continuous release of chemokines because such chemokines recruit more immune components to the site of inflammation.

Hancock expressly stated that RANTES and respective receptors can be associated with acute rejection. To prevent this increase of chemokines the Hancock group included an immunosuppressant to reduce the immune response. The list of immunosuppressive agents is set forth in paragraphs [0060] and [0061] and includes a multiplicity of different choices, as shown below and recreated from Hancock:

> **[0060]** The term "immunosuppressive agent", as used herein, refers to compounds which can inhibit an immune response. The immunosuppressive agent used in the invention can be a novel compound or can be selected from the compounds which are known in the art, for example, calcineurin inhibitors (e.g., cyclosporin A, FK-506), IL-2 signal transduction inhibitors (e.g., rapamycin), glucocorticoids (e.g., prednisone, dexamethasone, methylprednisolone, prednisolone), nucleic acid synthesis inhibitors (e.g., azathioprine, mercaptopurine, mycophenolic acid) and antibodies to lymphocytes or antigen-binding fragments thereof (e.g., OKT3, anti-IL2 receptor). Novel immunosuppressive agents can be identified by those of skill in the art using suitable methods, for example, screening compounds for the capacity to inhibit antigen-dependent T cell activation.
>
> **[0061]** The immunosuppressive agent used for co-therapy (e.g., co-administration with an antagonist of CCR5 function) is preferably a calcineurin inhibitor. More preferably the immunosuppressive agent used for co-therapy is cyclosporin A.

Specifically, the Hancock group administers the immunosuppressive agent to lower the level of chemokines and prefers the use of cyclosporin A to induce this result. Chemokines are considered to be pro-inflammatory compounds and Hancock requires the reduction of an immune response to insure that the graft recipient does not reject the transplanted grafts.

According to the Office:

Hancock teach a method for inhibiting the rejection of transplanted grafts comprising an effective amount of an antagonist of CCR5 and an effective amount of an immunosuppressive agent (see abstract and claims 1, 6 and 13). Immunosuppressive agents include rapamycin (see paragraph 60; addresses claims 1 and 3). AND Hancock does not teach TAK 779 (claims 1, 5 and 6).

Baba et al. teaches that TAK-779 is a small-molecule, nonpeptide that is a specific CCR5 antagonist (see title and abstract).

To one of ordinary skill in the art at the time of the invention would have found it obvious and motivated to combine the compositions of Hancock et al. and TAK 779 because TAK 779 is a small molecule that specifically antagonizes CCR5.

Thus, it is the Office's view that all the subject matter recited in applicants' claim 1 is disclosed by Hancock except for the CCR5 antagonist TAK 779, as described by Baba. Baba provides for the use of a CCR5 antagonist that sits on the CCR5 receptor and inhibits binding of HIV and stops the access of the virus to the receptor. However, it should be noted that Baba is attempting to treat HIV and certainly does not teach, suggest or desire the use of an immunosuppressant compound as taught by Hancock.

The Office proposes that the teachings of these two disparate references render the presently claimed invention as obvious. Applicants disagree and stress that Hancock and Baba are not analogous art and there is no suggestion that a skilled artisan would make a modification of Hancock with the CCR5 antagonist of Baba in the manner proposed by the Office.

Initially, it should be noted, as stated above, applicants' invention relates to a composition that causes an increase in chemokines and Hancock expressly states that immunosuppressive agent is used to lower the level of chemokines to rejection of the tissue grafts. It is well known that maintaining grafted tissues involves the use of compounds that inhibit the immune system. Clearly, a skilled artisan, reading Baba and looking for an HIV treatment, would not consider looking in the field of graft rejection which requires reducing immune responses because an HIV infected individual needs to maintain a healthy and active immune system.

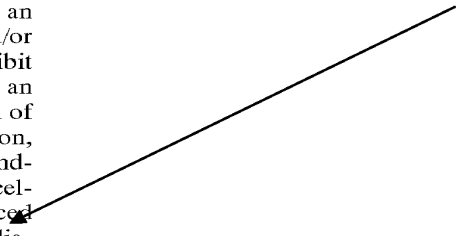
It is well settled in the law that in order to rely on a reference as a basis for rejection of the applicants' invention, the reference must either be in the field of the applicants' endeavor or, if not, then be

reasonably pertinent to the particular problem with which the inventor was concerned. (*See In re Deminski*, 230 USPQ 313, (Fed.Cir. 1986))

Further, the Office has not shown that a person of ordinary skill, seeking to solve a problem of treating an HIV infected individual, would reasonably be expected or motivated to look to method for treating graft rejections. The combination of elements from non-analogous sources, in a manner that reconstructs the applicants' invention but only with the benefit of hindsight, is insufficient to present a *prima facie* case of obviousness. *In re Oetiker,* 24 USPQ2d 1443, (Fed. Cir. 1992) Thus, reduced to the basics, one reading Baba and interested in treating HIV and attempting to save an already failing immune system would not look to Hancock which is attempting to suppress an active immune system to protect newly grafted tissue from rejection.

The Office's contention that Hancock teaches an effective amount of the G1 phase arresting agent to increase concentrations of extracellular beta-chemokines is not supported by the actual disclosure of Hancock. The Hancock reference only discusses a therapeutic effect that relates to stopping graft rejections. The mention of a therapeutic effect cannot be extended to increasing levels of chemokines especially when the Hancock reference provides for reducing immune responses. It is fundamental that the induction of chemokines is necessary for a healthy and normal immune response and chemokines are considered to be proinflammatory mediators. From paragraph [0068], recreated below from Hancock, it is evident that Hancock is interested in inhibiting the induction of proinflammatory mediators which is the exact opposite as that of the present invention.

[0068] An "effective amount" of a CCR5 antagonist is an amount sufficient to achieve a desired therapeutic and/or prophylactic effect, such as an amount sufficient to inhibit graft rejection. For example, an effective amount is an amount sufficient to inhibit a (i.e., one or more) function of CCR5 (e.g., CCR5 ligand-induced leukocyte migration, CCR5 ligand-induced integrin activation, CCR5 ligand-induced transient increase in the concentration of intracellular free calcium $[Ca^{2+}]_i$ and/or CCR5 ligand-induced secretion (e.g., degranulation) of proinflammatory mediators), and thereby inhibit graft rejection. An "effective amount" of an additional therapeutic agent (e.g., immunosuppressive agent) is an amount sufficient to achieve a desired therapeutic and/or prophylactic effect (e.g., immunosuppression).



Thus, Hancock never envisioned increasing the levels of an immune response and the Office may not speculate on such an effect.

Applicants insist that this rejection is similar to an "obvious to try" rejection. It is important for the Office to review the "*In re Kubin*" ruling decided on April 3, 2009 because it provides guidance showing that the presently claimed invention is not obvious. (See *In re Kubin*, 90 USPQ2d 1417, (Fed. Cir. 2009)) Specifically, the *Kubin* Court revisited the *In re O'Farrell* decision (*In re O'Farrell*, 853 F.2d 894(Fed Cir. 1988)) and discussed that to differentiate between proper and improper applications of "obvious to try," the O'*Farrell* Court outlined two classes of situations where "obvious to try" is erroneously equated with obviousness under §103. In the first class of cases:

> what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful.

In such circumstances, wherein metaphorical darts would be thrown at a board filled with combinatorial prior art possibilities, courts should not succumb to hindsight claims of obviousness.

The second class of *O'Farrell's* impermissible "obvious to try" situations occurs where

> what was "obvious to try" was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.

Notably, the combination of references provides no guidance for combining a G1 phase arresting agent with an antiviral agent that inhibits entry of HIV into the T-cell. Importantly, applicants' invention is not merely a composition including a G-1 phase arresting agent and HIV entry inhibitor, but instead is a novel and nonobvious composition that increases the level of chemokines and the positive immune response concomitant with such increase. No prior art suggests this and that which is unknown cannot be obvious.

Importantly, applicants have provided proof of the effectiveness of the presently claimed combination that not only shows increased levels of chemokines but reduced levels of HIV virus. The proposed combination of the cited references does not teach or suggest such a composition or such benefits.

Applicants have surprisingly found that the addition of RAPA increases the level of chemokines as shown in Figure 8A, recreated below:

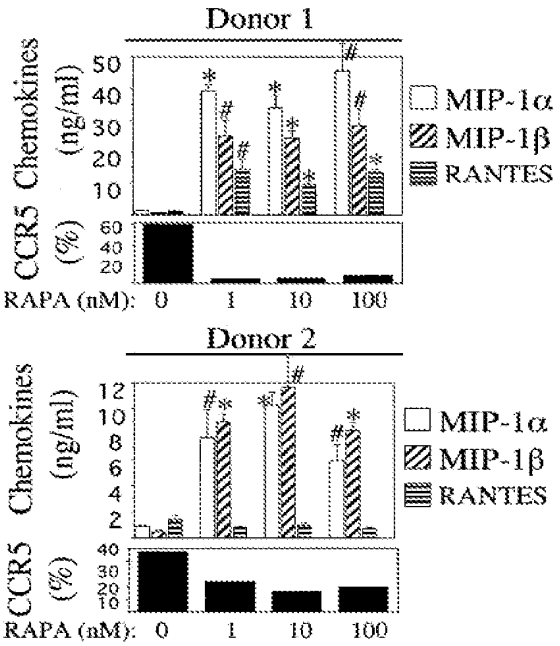


Figure 8A

As the Court stated in *Interconnect Planning Corp. v. Feil,* 227 USPQ 543 (Fed. Cir. 1985) "The invention must be viewed not with the blueprint drawn by the inventor, but **in the state of the art that existed at the time.**" (Emphasis added.) The state of the art existing at the time of the invention was characterized by understanding that combining a CCR5 antagonist and immunosuppressive agent (Hancock) caused a reduction of chemokines. Nothing in the prior art hinted at an increase in chemokines.

Thus, in light of the above discussion, applicants request reconsideration and the withdrawal of this rejection under 35 U.S.C. §103(a).

2. Claims 1, 3, 5-7 and 10 were rejected under 35 U.S.C. §103(a) as being unpatentable over Vezina in view of Baba. Applicants insist that such a combination does not establish a *prima facie* case of obviousness.

According to the Office, one skilled in the art would combine the teachings of Vezina with Baba and such a combination renders the presently claimed invention as obvious. Applicants disagree and insist that a

skilled artisan reading the two references and the individual teachings of each would not consider combining them.

Initially, it should noted that Vezina teaches that cytotoxic levels of a rapamycin eliminate T-cells. As stated in Vezina and recreated below, cytotoxic levels of rapamycin were used to eliminate the cellular reservoir of hosts cells (CD4+, monocytes, macrophages and lymphocytes) of HIV.

> The present inventor now addresses the HIV replication problem by eliminating the cellular reservoir of host cells ($CD4^+$ monocytes, macrophages and lymphocytes) of HIV by using cytotoxic doses of rapamycin for limited periods of time. Nowhere has there ever been an indication or suggestion that rapamycin may have an effect on the virus presence itself through selective suppression of the host cell population.

Thus, one of the major effects of the Vezina reference is the loss of CD4+ cells. However, applicants know that the loss of CD4+ cells causes increased problems for subjects suffering with HIV because of the diminishment of immune response.

Reviewing the results of Example 2 of Vezina shows the emphasis on the inhibition of CD4+ cell replication:

> EXAMPLE 2.
> *In vitro incubation of rapamycin with $CD4^+$ human cells uninfected and infected with defective HIV-1.*
>
> TEST CELL CULTURES:
>
> Different concentrations of rapamycin were tested on the following cell lines in culture:
> -MT-4 ($CD4^+$ T lymphocytes);
> -MT-2 (MT-4 cells infected with a defective HIV-1 HTLV III_B [Harada et al., Science 229: 563-566, 1985, enclosed herewith by reference];
> -U937 (monocyte) (ATCC CRL-1593); and
> -URCS (U937 infected with a defective HIV-1 HTLV III_B, R3 strain [Roulerice et al., J. Virol., 64, 1745-1755, 1990, enclosed herewith by reference].

It is evident from the results set forth in Table 3 of Vezina, as shown below, that replication of infected cells CD4+ cells (MT-2 and UHC8) was inhibited, and thus, **less** T-cells are available to the immune system to combat the HIV virus. This is a problem because of the diminishment of immune T cells that are required to overcome the negative effects of HIV.

Results are presented in Table 3 as percent of inhibition of cellular growth of infected and uninfected host cells:

Table 3

Rapamycin (ng/ml)	MT-4 (% inhibition)	MT-2 (% inhibition)	U-937 (% inhibition)	UHC8 (% inhibition)
0	0	0	0	0
0.01	35	49	24	46
0.1	78	85	78	83
1	87	–	–	87
10	81	85	78	81
100	82	86	82	82

RAPA toxicity

The toxicity of the compound at 100 ng/ml through 0.1 ng/ml was greater than about 80% cellular inhibition both for uninfected and infected cells. Although, at 0.01 ng/ml, the infected cells seemed slightly more sensitive to rapamycin than the uninfected cells, it seems that the anti-HIV effect of rapamycin may be due primarily to its toxicity on the replication of the host cells (lymphocytes and monocytes).

Thus, a skilled artisan reading Vezina would understands that Vezina teaches that the replication of T cells is decreased by the toxicity of rapamycin and notes that a subject can be depleted of an important component of the immune system.

As described above, Baba provides for the use of a CCR5 antagonist that sits on the CCR5 receptor and inhibits binding of HIV, thus stopping the access of the virus to the receptor. The reference discusses the use of an assay to show that the CCR5 antagonist has greater affinity for the receptor than RANTES which is the natural binding ligand for the CCR5 receptor. Thus, the CCR5 antagonist of Baba is effective only if there are viable T-cells that have expressed the CD4+ receptor and the CCR5 receptor.

Applicants question why a skilled artisan would combine the Vezina and Baba references especially because Baba **must have viable T cells with CCR5 receptors** and Vezina causes the **elimination of T-cells that express the CD4 and CCR5 receptors.**

Applicants remind the Office that under Graham, and as required by MPEP §§ 2111 and 2141.02, the Office must ascertain the differences between the claimed invention and the prior art, and must consider both the invention and **the prior art as a whole**. Thus, even in light of the *KSR* decision, **the Office must consider the inventions of any cited references in their respective entireties.** Certain individual features from the references may not be arbitrarily chosen (while equally arbitrarily discarding other disclosed features) to merely lump together disparate features of different references as a mosaic in an attempt to meet the features of the rejected claims. Thus, the Office is not allowed to pick and choose just certain parts of different references and combine them, **but instead, the references in their entirety must be considered.**

Further, MPEP § 2143.01 V – VI states that:

> "If proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. … [and] If the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims prima facie obvious."

According to the Court in *In re Gordon,* 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984), if proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification and the Office has not established a *prima facie* case of obviousness. Further, the ruling in *In re Ratti*, (270 F.2d 810 (CCPA 1959)) states that where a proposed modification would change the **principle of operation of the prior art invention being modified**, then the teachings are not sufficient to establish a *prima facie* case of obviousness. The Board recently reiterated in *Ex Parte Vito Cellini*, (Appeal 2008-4104, BPAI 2008), and stated that "a change in the basic principles" refers to change that is fundamental in scope so as to **relates to scientific or technical principles of operation.**

As stated above, Vezina teaches the reduction of the CD4+ T-cells, and thus, applicants question why a skilled artisan would consider adding a compound from Baba that needs to bind to a CCR5 receptor on the T-cell when Vezina is constantly reducing T-cells. If the landing sites are being reduced by cytotoxic levels of RAPA, as described by Vezina, then the compound of Baba will not have receptors to bind with. Thus, Baba will no longer function as intended. As such, the proposed combination does not establish a *prima facie* case of obviousness because the combination of references fundamentally change the "basic principals" under which the prior art was designed to operate.

The present invention avoids the shortcomings of Vezina because the number of CD4 containing T-cells is not reduced. Instead, the T-cell viability is maintained with an increase of chemokines which provides for the maintenance of the cell viability and also a reduction of HIV replication, as shown in Figure 5 A, of the instant application recreated below.

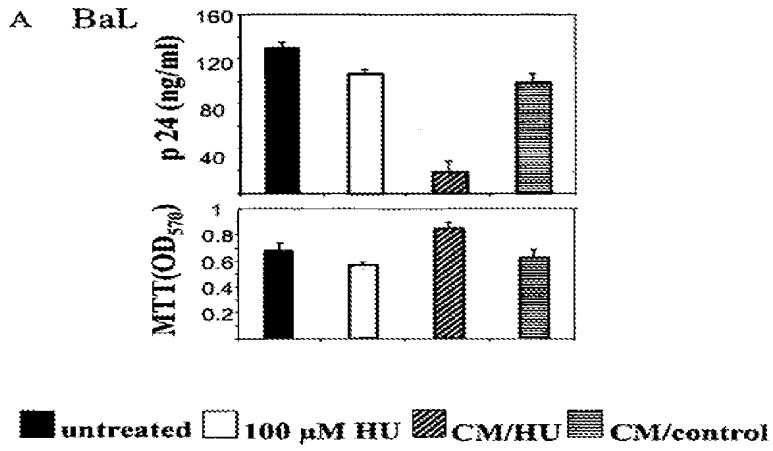
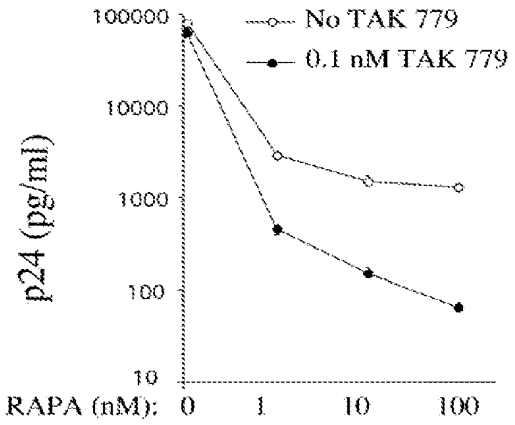


Figure 5

Figure 5A shows the results of using hydroxyurea as the G1 phase arresting agent. The antiviral activity of the supernatants collected from cultures of PBMCs that had been exposed to 100 μM HU for 7 days [supernatants referred to as conditioned medium (CM)] was evaluated in PBMCs infected with HIV-1 BaL and HIV-1 IIIb. Briefly, PHA-activated PBMCs were infected with each virus at 100 tissue culture 50% infective dose units ($TCID_{50}$)/10^6 PBMCs or 10 $TCID_{50}$/10^6 PBMCs for 2 h at 37°C. Infected cells were cultured in IL-2 medium alone, IL-2 medium with 100 μM HU, IL-2 medium containing 50% supernatant from HU-treated PBMCs (CM/HU), or IL-2 medium containing 50% supernatant from control-treated PBMCs (CM/control). On day 3 after infection, culture medium was replaced with fresh medium of the same kind as on day 1. Viral growth (measured by p24 levels in the supernatant) and cell viability (assayed by MTT) were determined on day 7 after infection. It is evident that using the G1 phase arresting agent, hydroxyurea, maintained the cell viability including T-cells and also reduced viral growth.

Applicants have provided proof of the effectiveness of the presently claimed combination that includes a G1 phase arresting agent in combination with an agent that inhibits entry of HIV into the cell. As shown

in Figure 11 of the present application, and recreated below for ease of discussion, it is evident that there is a three-log reduction in viral replication with the combination of RAPA and TAK 779.



According to the Office, a skilled artisan would read the Baba reference and immediately disregard use of AZT of Vezina and instead use TAK 779 even if Vezina never shows the effectiveness of such combination. Applicants question where in either reference is there any suggestion that the proposed combination would be effective? There is none and the Office cannot speculate on such a combination, unless of course the Office is using applicants' specification as a blue print to go looking for components. This type of hunting expedition would be using impermissible hindsight which is still considered unacceptable because the *KSR* Court expressly stated that a flexible TSM test remains the primary guarantor against **a non-statutory hindsight analysis, such as, the Office is using in the presently claimed invention.**

Applicants submit that the Office did not establish a *prima facie* case of obviousness, and as such, request that the rejection under 35 U.S.C. §103(a) be withdrawn.

Rejoinder of Method Claims

In accordance with Office guidelines recited in MPEP Section 821.04, when the elected product claims are found to recite patentable subject matter then the method claims that have been withdrawn may be rejoined and examined in this one application provided the method of use recite limitations corresponding to those found to be patentable during examination of the elected invention. As such, when the product claims are found to recite patentable subject matter, non-elected method claims 11, 12, 15-18, 23, 25, 27, 30, 33, 35, and 37-47 should be taken up for examination.

Petition for Extension and Fees Payable

Applicants petition for a one month extension, extending the three month deadline of December 22, 2010 to January 24, 2011 (since January 22, 2011 falls on a Saturday), wherein the fee is being paid by electronic transfer. No additional is due for entry of this amendment, however if a fee is found due, the Commissioner is authorized to charge such fee to Deposit Account No. 13-4365 of Moore & Van Allen.

Conclusion

Applicants have satisfied the requirements for patentability. All pending claims are free of the art and fully comply with the requirements of 35 U.S.C. §112. It therefore is requested that Examiner Carter reconsider the patentability of the pending claims in light of the distinguishing remarks herein, and withdraw all rejections, thereby placing the application in condition for allowance. If any issues remain outstanding incident to the allowance of the application, Examiner Carter is requested to contact the undersigned attorney at (919) 286-8089.

Respectfully submitted,

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